A STUDY OF SOME PECULIAR TROPICAL RISK FACTORS FOR PROTEINURIA AS MARKER OF CHRONIC KIDNEY DISEASE IN A RURAL COMMUNITY IN ONDO STATE, SOUTH-WEST NIGERIA.

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ABSTRACT
BACKGROUND: *The role of herbal remedies and Non-Steroidal Anti-inflammatory Drugs in the development and progression of chronic kidney disease are yet to be fully studied in our environment despite their indiscriminate use. We set out to determine the prevalence and pattern of use of herbal remedies and NSAIDs and their relationship (if any) to chronic kidney disease.*

METHODS: *Adults at a screening exercise in a village in Ondo State, Nigeria were studied. Their bio-data, history of herbal usage and NSAIDs, cigarette smoking, alcohol intake, diabetes mellitus and essential hypertension were obtained. Their blood pressure and anthropometry were measured. Urinalysis was conducted with Combi-Uriscreen®. Data was analysed using SPSS 20.*

RESULTS: *One hundred and sixteen subjects were studied (M:F, 1:1.8). 51.7% were farmers. Their mean age was 42.5±14.7 years (range, 17-78 years). Their mean systolic and diastolic blood pressures were 125.2±20.4mmHg and 77.3±12.3mmHg respectively. Their mean body mass index was 26.2±6.0 kg/m^2.*
Usage of herbs was found among 78.4% of subjects. 68.1% used NSAIDs, 11.2% had a history of cigarette smoking, 25.0% used alcohol, 50.0% had pre-hypertension, 28.0% had essential hypertension and 7.8% had diabetes mellitus. Undiagnosed hypertension was present in 24.1%. Proteinuria (ranging between 100mg/dl and 500mg/dl) was present in 12.5% of the subjects. Central obesity was present in 21.9% of the subjects.
There was a significant association between proteinuria and use of herbs (p=0.023, chi square 5.188), use of NSAIDs (p=0.01, chi square 6.722), and pre-hypertension (p=0.039, chi square 4.261).

CONCLUSION: *The rates of use of herbal remedies and NSAIDs in the rural community are high. Our study suggests that they may cause significant proteinuria among users. There is therefore a need to conduct more high powered studies on this subject.*

KEYWORDS: herbal concoction, renal failure, tropics, proteinuria, Nigeria

INTRODUCTION

Chronic kidney disease (CKD) remains largely a myth in Africa because of low awareness level [1]. Hypertension and diabetes mellitus (DM) are proven risk factors and causes of CKD [2]. Other factors which are more peculiar to Africans such as use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and herbs are usually linked to acute renal dysfunction [3]. Recent data however reveal that these are now considered as 'initiation factors' for CKD even though they continue to be used indiscriminately in Africa due to inadequate healthcare services [4-6]

We therefore set out to determine the prevalence of use of herbal remedies and NSAIDs (aside other factors) in a rural community in South West Nigeria and their relationship (if any) to proteinuria.

METHODOLOGY

Study location: *Sasere* is one of many small villages in Ondo East Local Government Area of Ondo State in South–West Nigeria. It has an approximate population size of about 850 people. It represents the typical rural setting in contemporary sub-Sahara Africa; predominantly agrarian, deficient of basic social amenities, poor road network and linkage to the major cities, deficient health infrastructure and medical personnel. It is surrounded by other villages including *Aruwa, Solo, Lugbameji, Letule, Kiseye, Toribo* and *Awaiye* all within Ondo East Local Government Area with a population size of 76,092 as of 2006 Nigerian population census [7].

Study design: This was a cross-sectional study of consecutive adults = 17 years who presented at a community screening exercise during a medical outreach programme. At least 3 sensitization visits were made to the community leaders before the study. A house-to-house sensitization was also conducted. Ethical approval was received from the Ondo State Ministry of Health.

All participants were recruited after an informed consent. Their bio-data, history of smoking, alcohol intake, consumption of herbal concoction, use of Non-Steroidal Anti-Inflammatory Drugs, DM and essential hypertension were obtained. Their blood pressure (BP) was measured on the right arm using the *Accosons (Germany)* mercury sphygmomanometer with a standard cuff size and subjects in sitting position after about 5 minutes of rest. Essential hypertension was classified according to the seventh Joint National Committee Report on Detection, Evaluation and treatment of High Blood pressure (JNC 7) report [8]. Subjects with elevated blood pressure were asked to rest for at least one hour and the measurement was repeated before the exercise was concluded. All subjects were presented with the question, "Have you ever been told by a doctor or other health professional that you have high BP?" Hypertension was defined by a measured BP of = 140/90 mmHg and/or use of antihypertensive. Pre-hypertension was defined by Systolic BP of 120-139mmHg and Diastolic BP of 80-89mmHg [4]. Respondents who said 'No' to the question on hypertension but had BP reading of = 140/90mmHg were labelled as having "undiagnosed hypertension".

Herbs (or herbal mixtures) in this study was defined as medications derived from single or a mixture of plants, plant materials or herbs that may or may not be mixed with other chemicals. Subjects who consumed herbal mixtures regularly for at least 5 days per week were considered to have significant exposure in this study. Subjects who had used a mixture of 2 or more of any NSAIDs such as ibuprofen, naproxen, piroxicam, indomethacin, or diclofenac (regardless of the brand) including caffeine daily or nearly every day within the last 60 days of study were reported as positive for use of NSAIDs.

Body weight was measured (after removal of footwear) with subjects in light clothing to the nearest 0.1 kg using bathroom scale (*HANA, China*). Height was measured with the subject standing without shoes on a firm, level surface at right angle to a vertical height bar. Readings were taken to the nearest 0.5cm. Body mass index (BMI) was calculated using the formula, weight/height^2. The waist circumference (WC) was measured using the mid-point between a line drawn from the costal margin and the anterior superior iliac spine while the hip circumference (HC) was measured using the transtrochanteric line by means of non-stretch measuring tapes with subjects in the erect position. Central obesity was defined as waist circumference (WC) = 94cm and = 80cm for males and females respectively, using the International Diabetes Federation criteria [9].

Spot urinalysis was carried out using the *Combi-Uriscreen® 10SL* test strips on clean catch mid-stream urine samples after having given verbal instructions on the modality of collecting midstream urine specimen to the subjects at the screening centre. Those with proteinuria of = 1+ (30mg/dl) were referred to the Kidney Care Centre for a repeat test.

ANALYSIS

Data was analysed using SPSS version 20. Descriptive variables such as age, anthropometric measurements and BP readings were presented as frequencies, percentage and mean (± standard deviation). One sample t-test was used to determine significant differences between continuous variables. Test of association between categorical variables was determined by chi square. The p value was regarded as significant at $p < 0.05$ at a Confidence Interval of 95%.

RESULT

A total of 116 subjects were studied. There were 2 males and 74 females with a male to female ratio of 1 to 1.8. There were 60 (51.7%) farmers and 23 (19.8%) traders among others (table 1).

Their mean age was 42.5±14.7 years with an age range of 17 to 78 years. Their mean systolic and diastolic BP was 125.2±20.4mmHg and 77.3±12.3mmHg respectively. Their mean BMI was 26.2±6.0 kg/m^2. The mean WC for males and females were 77.5±11.2cm and 82.9±13.6cm respectively.

Table 1: Demographic characteristics of subjects

Demographic parameters	Frequency	Percentage
Gender		
Male	42	36.2%
Female	74	63.8%
Age group (years)		
Young (17-39)	55	47.4%
Middle age (40-59)	40	34.5%
Elderly (>60)	21	18.1%
Occupation		
Civil servant	2	1.2%
Clergy	4	2.5%
Engineer	1	0.6%
Farmer	**60**	**51.7%**
Hairdresser	3	1.9%
Unemployed	4	2.5%
Student	4	2.5%
Tailor	5	3.2%
Teacher	5	3.2%
Trader	**23**	**19.8%**
History of cigarette smoking		
No	100	86.2%
Yes	13	11.2%
No response	3	2.6%
History of use of alcohol		
No	84	72.4%
Yes	29	25.0%
No response	3	2.6%
History of use of herbs		
No	25	21.5%
Yes	91	78.5%
History of use of NSAIDs		
No	35	30.2%
Yes	79	68.1
No response	2	1.7%
History of diabetes mellitus		
No	101	87.1%
Yes	9	7.8%
__	6	5.1%
History of hypertension		
No	89	76.7%
Yes	27	13.3%
Waist circumference above cut off (IDF criteria)		
No	89	78.1%

One hundred of the subjects consented to BP check. Fifty (50.0%) had pre-hypertension, 28 (28.0%) had hypertension. Thirteen (11.2%) had a history of cigarette smoking, 29 (25.0%) used alcohol, 91 (78.4%) used herbs, 79 (68.1%) used NSAIDs, 9 (7.8%) had DM. Twenty seven (23.3%) affirmed that they had essential hypertension while 83 (71.6%) said they were not hypertensive. Among those who affirmed they were not hypertensive, 20 (24.1%) had BP in the hypertensive range. Out of 107 urine samples that were tested, 14 (12.5%) had proteinuria ranging between 2+ (30mg/dl) and 3+ (500mg/dl) (table 2). 25 (21.9%) of the subjects had central obesity.

Table 2: degree of proteinuria among subjects

Proteinuria (mg/dl)	**Frequency**	**Percentage**
Negative	47	43.9
Trace (5-20mg/dl)	21	19.6
1+ (30mg/dl)	25	23.4
2+ (100mg/dl)	12	11.2
3+ (500mg/dl)	2	1.3
Total	**107**	**100.0%**

Table 3 showed that significantly more females used herbal remedies and NSAIDs. Subjects who were aware of their BP showed safer BP status (table 4).

Table 3: Gender differences in CKD risk factors among subjects

Parameter	Male	Female	P value	Chi square
herbal remedies	34 (37.4%)	57 (62.6%)	0.016	5.813
NSAIDs† use	32 (39.0%)	50 (61.0%)	0.047	3.951
Pre-hypertension	23 (46.0%)	27 (54.0%)	0.572	0.320
Hypertension	8 (28.6%)	20 (71.4%)	0.023	5.143
Central obesity	2 (8%)	23 (92%)	0.000	17.64

†non-steroidal anti-inflammatory drugs

Table 4: Hypertension awareness and blood pressure status among subjects

Blood pressure (mmHg)	Blood pressure awareness status		t-test	p-value	95% Confidence Interval	
	Aware	Not aware				
[illegible]	115.98 (±11.38)	149.40 (±19.39)	-7.322	0.000	-42.85	-23.98
DBP‡ (mean±SD)	71 (±7.16)	88.75 (±8.66)	-9.715	0.000	-22.65	-14.95

†systolic blood pressure; DBP, ‡diastolic blood pressure; p value is significant at $p<0.05$

Table 5 shows a significant association between proteinuria and use of herbs (p=0.023, chi square 5.188), use of NSAIDs (p=0.01, chi square 6.722), and pre -hypertension (p=0. 039, chi square 4.261).

Table 5: Relationship between risk factors of CKD and proteinuria among subjects

Aetiology/risk factor	N†	Proteinuria (frequency, percentage)	P value	Chi square
Gender	116	39 (36.5%)	0.150	2.077
Herbs	85	53 (62.4%)	0.023*	5.188
NSAIDs	72	47 (65.3%)	0.01*	6.722
Hypertension	25	12 (48%)	0.841	0.04
Pre-hypertension	46	16 (34.8%)	0.039*	4.261
Smoking	13	6 (46.2%)	0.782	0.077
Central obesity	25	13 (52%)	0.297	1.087
Alcohol	27	12 (44.4%)	0.564	0.333

†number of subjects tested; P value is significant at <0.05.

DISCUSSION

Herbal Remedies: We found that a high proportion of the subjects (78.4%) used herbal mixture. The prevalence observed in our study is higher than 75% reported by Oluyombo *et al* among rural dwellers in Osun State, South West Nigeria and close to over 80% found among populations in some Asian and African countries where use of herbs is renowned [10-12]. This practice is common place in sub-Sahara Africa as rural communities lack access to good healthcare infrastructure and medical personnel with these unrefined concoctions are often prepared and administered by traditional healers who in most cases double as community elders, or spiritual leaders with close family ties to their 'clients' unlike the more professional services offered by orthodox healthcare workers who are often perceived as impersonal and distant by the people. Other important factors for a high patronage of herbal remedies include their relatively low costs, socio-cultural acceptability, ignorance and poverty [13,14]
Our current figure is higher than results obtained from earlier studies conducted among urban residents in Lagos, South West Nigeria (66.8%) and Enugu, South East Nigeria (69.4%) [15,16]. This may be a further reflection of the dearth of qualified pharmacists in the rural areas compared to the urban settings.

Non-Steroidal Anti-Inflammatory Drugs: Our study showed that 68.1% of subjects used NSAIDs. This is far higher than a prevalence of 25.8% found in one study among rural dwellers in Central Nigeria and the 20% by Oluyombo *et al* in 2013 [10,17]. The disregard for safety precautions in NSAIDs is exemplified by a survey conducted by Ingrasciotta *et al* among 1,989 CKD patients in Southern Italy where 56.3% of the subjects were reported to have received at least one NSAID for various ailments despite their CKD status [18]. In another study among patients attending the General Out-Patient Department spread across three tertiary hospitals in Nigeria on treatment for chronic non-cancer pain, 73% were placed on NSAIDs [19]. In that study, there was no documented attempt to determine the baseline renal function of the subjects.

Proteinuria, marker of chronic kidney disease:
Proteinuria was found among 12.5% of the subjects in our study. This is slightly higher than the global prevalence of 7% [20] It is however comparable to values of between 12.4% and 19.4% obtained by different study groups in Nigeria [21-23]. It is important to note that despite a relatively high prevalence of essential hypertension (28%) and DM in our study (7.3%), there was no significant association between these two disorders and proteinuria whereas there was a significant association between proteinuria and consumption of herbal concoction and use of NSAIDs.

Relationship between herbal remedies and proteinuria:
Our study showed a significant association between consumption of herbal remedies and presence of proteinuria. The indiscrete use of herbs has been associated with risk of renal toxicity [24,25]. For instance, interstitial nephritis and urothelial tumours have been known to arise directly from the effect of certain Chinese herbal remedies containing aristolochic acid [26]. Other herbs have been associated with acute tubular necrosis, cortical necrosis and interstitial nephritis [27]. Indeed, one study in a Nigerian family practice population in Ile-Ife, South West Nigeria demonstrated a significant association between habitual consumption of herbs and CKD [28].

Relationship between NSAIDs and proteinuria:
A significant association was also demonstrated between use of NSAIDs and presence of proteinuria in our study. Gooch *et al* have shown that there is a linear progression of CKD in association to chronic use of high dose NSAIDs among an elderly group of non-CKD subjects [29]. Whether age, a known risk factor for onset of CKD contributed to the outcome of that particular study was not highlighted. Also, some epidemiologic studies have associated NSAIDs with acute interstitial nephritis and progressive renal impairment [30,31]. Even though pockets of studies in the past showed no association between the use of analgesic preparations and increased risk of renal dysfunction, analgesic nephropathy can result from NSAIDs [32,33]

Other risk factors:

Pre-hypertension had a positive association with proteinuria in our study. This has been demonstrated in a study by Deidra *et al* where the prevalence of CKD was as high as 17.3% in a US population with pre-hypertension [34].

Our study showed that 28.0% of the subjects were hypertensive. This figure doubles the result from a similar rural setting in Nigeria with a prevalence of 12.5% as far back as 2010 **and compares to 30.0%**

from Oluyombo *et al* reported only 2 years ago [10,35]. This may indicate increasing prevalence of essential **hypertension in our environment.**
The prevalence of undiagnosed hypertension was 24.1% in this study as among 83 subjects who claimed that they were not hypertensive, 20 (24.1%) were found to have BP in the hypertensive range. This figure is comparable to 29.5% obtained among a petrochemical industrial population in China and the 28.0% among a United States population observed between 1999 and 2004 [36,37]. Our s**ubjects with awareness of their BP status had significantly lower BP readings below the cut off for hypertension (as defined by JNC 7 report) unlike those who were not aware. Studies have shown that undiagnosed hypertension predisposes subjects to increased cardiovascular risks and CKD [38].**

In our study, 7.3% of subjects had historical evidence of DM. This figure is higher when compared to the Nigerian national prevalence of 2.7% published in 1997[39]. However, more recent studies have indicated a rise in the prevalence of DM to levels ranging between 4.6% and 10.3% across Nigeria[40,41]. Our study may also be evident of an increasing prevalence of DM in our society.

Conclusion and recommendations: In conclusion, the rates of use of herbal remedies and NSAIDs among our subjects in the rural setting are high. The results of our study suggest that they may contribute significantly to higher rates of proteinuria (marker of CKD) in our population. There is therefore a need to conduct more high powered studies on this subject which will include use of more accurate measures for determination of renal function, quantification of NSAIDs and analysis of the toxicity of the herbs.

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